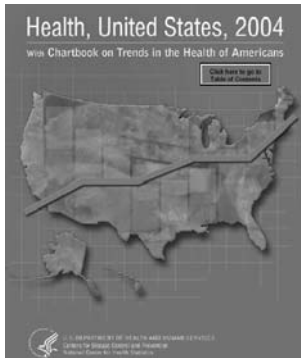


Treatment of Hypertension

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<http://www.cdc.gov/nchs/data/hus/04trend.pdf#067>

Hypertension

- ◆ 50 million Americans may have HTN
 - YOU have a 90% lifetime risk of developing hypertension
- ◆ Hypertension is *not a disease*, it is an *asymptomatic risk factor!*
- ◆ Major contributor to the development of CHF

Hypertension

Table 2. Trends in awareness, treatment, and control of high blood pressure in adults ages 18–74*

	NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY, PERCENT			
	II (1976–80)	III (PHASE 1 1988–91)	III (PHASE 2 1991–94)	1999–2000
Awareness	51	73	68	70
Treatment	31	55	54	59
Control†	10	29	27	34

Benefits of Treating HTN

- ◆ Significant reductions in morbidity and mortality due to cardiovascular disease (CHD, MI, CHF) and cerebrovascular disease (stroke)

HTN

- ◆ Systolic and Diastolic Pressure
- ◆ $BP = CO \times TPR$
 - » $CO = HR \times SV$
- ◆ Preload
- ◆ Afterload
- ◆ Venous dilation and constriction
- ◆ Arteriolar dilation and constriction

Defining HTN

◆Essential

-idiopathic, primary

◆Secondary

-renal dx

-thyroid

-hyperaldosteronism

-drugs

-RAS

-anemia

-pheochromocytoma

Defining HTN

◆Emergency vs. Urgency

◆“White Coat” hypertension

◆PIH vs Pre-eclampsia

Diagnostic Work-Up

◆Medical hx

◆Physical Exam

-Blood pressure measurement

-Examination of optic fundus

» Arterial narrowing, papilledema,
hemorrhages/exudates

-Laboratory tests

» Thyroid, Scr, BG, lipids, serum K+

» H & H, EKG, aldosterone

Lifestyle Modification

- ◆Weight reduction
- ◆Restriction of EtOH
- ◆Restriction of sodium (DASH diet)
- ◆Calcium and potassium
- ◆Tobacco avoidance
- ◆Exercise
- ◆Relax
- ◆Dietary fats

Hypertension: Keys to individualizing treatment

- ◆Hemodynamics of BP regulation
- ◆Pathophysiology of HTN
- ◆End-organ damage
- ◆Concomitant medical diseases
- ◆Demographics
- ◆ADRs/QOL
- ◆Compliance
- ◆Cost (Direct and Indirect)

Reasons for Treatment Failure

- ◆Non-compliance
- ◆Inadequate dosing
- ◆Wrong class choice
- ◆Body compensation
- ◆ADRs are exaggerated
- ◆Insufficient non-pharmacologic therapy
- ◆Inadequate monitoring

Non-Compliance with Anti-Hypertensive Therapy

- ◆ Cost
- ◆ Adverse Effects
- ◆ Complexity of Dosing
- ◆ Inadequate follow-up
- ◆ Lack of understanding of disease state
- ◆ PATIENT BELIEF!

Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VII)

- ◆ National High Blood Pressure Education Program
- ◆ NIH-NHLBI
- ◆ <http://www.nhlbi.nih.gov/guidelines/hypertension/index.htm>

JNC-VII Classification

- ◆ Normal: <120/<80
- ◆ Pre-hypertension: 130-139/80-89
- ◆ Stage 1 (Mild): 140-159/90-99
- ◆ Stage 2 (Moderate): >160/>100
- ◆ Stage 3 (Severe): Eliminated

Risk Stratification

◆Risk factors:

- » smoking,
- » dyslipidemia
- » diabetes
- » age >60
- » sex (males and post-menopausal females),
- » family hx in male < 55 or female < 65

◆Target organ damage:

- » heart disease
- » stroke or TIA
- » nephropathy
- » retinopathy

Goals of Therapy

- ◆Diagnose properly
- ◆Identify 2° causes
- ◆Identify risk factors
- ◆Identify target organ damage
- ◆Identify compelling indications
- ◆Select best agent

Goals of Therapy

- ◆General: 140/90
- ◆Diabetes or renal insufficiency: 130/80
- ◆Renal failure and proteinuria: 125/75

Other Considerations

- ◆ Young, no other CHD risk factors: 160/100
- ◆ White Coat Hypertension
- ◆ J-curve phenomenon: DBP <85 in CHD
- ◆ Isolated Systolic Hypertension
 - Diuretic or long-acting DHP CCA
- ◆ Non-pharmacologic measures (6-12 mos)
only: nl or pre w/o CI

Pharmacotherapy of Hypertension

- ◆ Thiazide Diuretics
- ◆ β -blockers
- ◆ ACE Inhibitors/A-II Antagonists
- ◆ Calcium Channel Blockers
- ◆ α blockers
- ◆ α - β Blockers
- ◆ Centrally acting agents
- ◆ Direct Vasodilators
- ◆ Combination Therapy

JNC-VII Recommendations

- ◆ “Stepped care is out”
- ◆ “Long-acting” drugs preferred
- ◆ Low-dose combinations may be appropriate
- ◆ Preferred 1st line drugs
 - Thiazide Diuretics
 - β -blockers
 - ACE-I, ARB, CCB

JNC-VII Recommendations

- ◆ Monotherapy for Stage 1 HTN
- ◆ Not good 1st line drugs:
 - Direct-acting vasodilators (hydralazine, minoxidil)
 - α_2 agonists (clonidine, guanfacine)
 - Peripherally acting adrenergic antagonists (Guanadrel, guanethidine)
 - Short-acting calcium channel antagonists

JNC-VII Recommendations

- ◆ In most cases, HTN does not need to be controlled acutely!
- ◆ If inadequate response (1-3 months)
 - Increase the dose
 - Switch to another class
 - Add another drug
 - » HCTZ is a good 2nd choice

Diuretics

- | | |
|--------------------------|-------------------|
| ◆Thiazides: HCTZ, et al. | ◆Loop Diuretics: |
| ◆Chlorthalidone | – furosemide, |
| ◆Metolazone | – bumetanide, |
| ◆Indapamide | – torsemide |
| ◆“Potassium Sparing” | – ethacrynic acid |
| – triamterene | |
| – amiloride | |
| – spironolactone | |

HCTZ

- ◆ My Pick
- ◆ Best for blacks, elderly, mild HTN
- ◆ Synergistic with ACE, β -blockers
- ◆ Dose: 12.5 - 50 mg (usually not > 25 mg)
- ◆ Protective against Hip Fractures
 - decreases urinary Ca^{++} excretion
 - increases BMD

Potassium Sparing Diuretics

- ◆ Potassium sparing - in combo with HCTZ
 - Do not work well alone in tx of HTN
 - Caution use with ACE-I
 - Caution use in Renal Insufficiency
 - Spironolactone
 - » hyperaldosteronism
 - » CHF, ascites
 - Hyperkalemia

Other Diuretics

- ◆ Chlorthalidone ---> Hypokalemia
- ◆ Metolazone, Indapamide - better in renal insufficiency

Loop Diuretics

- ◆ **MOA:**
 - Block reabsorption of Cl^- in ascending LOH
- ◆ **Short acting**
- ◆ **Reserved for renal insufficiency**
- ◆ **Equivalencies exist between drugs**
- ◆ **Cross-sensitivity with sulfa drugs**

Diuretics Adverse Effects

- ◆ **Hypokalemia/natremia**
- ◆ **Hyperkalemia (K^+ -spar)**
- ◆ **Hyperuricemia(T)(L)**
- ◆ **Glucose intolerance**
- ◆ **Postural hypotension**
- ◆ **Phototoxicity (L)**
- ◆ **↑ LDL/TG**
- ◆ **Sexual dysfunction**
- ◆ **Hyper(T)/hypocalcemia(L)**
- ◆ **Ototoxicity(L)**
- ◆ **Hypomagnesemia**

Beta Blockers

- ◆ **MOA:**
 - ↓ HR
 - ↓ contractility
 - ↓ renin output
- ◆ **Patient selection:**
 - whites, young, CHD, A-fib, migraine, post-MI, anxious, tachycardic
- ◆ **Properties**
 - Cardioselectivity
 - Intrinsic sympathomimetic activity (ISA)
 - Lipophilicity/Hydrophilicity

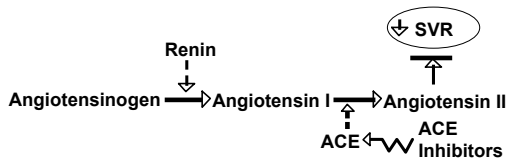
Adverse Effects

- ◆ Bradycardia
- ◆ Dizziness
- ◆ Bronchial constriction
- ◆ Fatigue
- ◆ Insomnia/bizarre dreams
- ◆ Depression
- ◆ Postural hypotension
- ◆ ↓ HDL, ↑ TG
- ◆ AV block
- ◆ Sexual dysfunction
- ◆ ↑ PVD
- ◆ Abrupt cessation

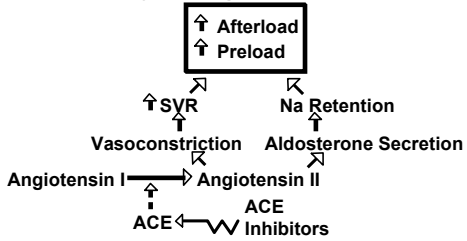
Beta Blockers

- ◆ Effect on Lipids
- ◆ Effect on sexual function
- ◆ Caution use in:
 - CHF, COPD, Asthma, IDDM
- ◆ My pick: Atenolol
 - Generic, inexpensive, hydrophilic, cardioselective, once-a-day

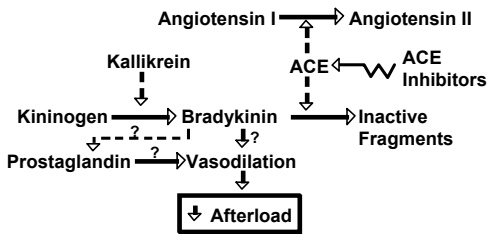
ACE Inhibitors Mechanism of Action



ACE Inhibitors Physiologic Effects



ACE Inhibitors Other Effects



ACE Inhibitors

- ◆ Response: Whites > Blacks
- ◆ DOC if concomitant DM, CHF
- ◆ Synergistic with HCTZ
- ◆ Most are once-a-day (Captopril BID-TID)

ACE Inhibitors

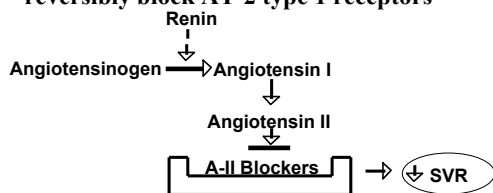
- ◆ DC diuretic prior to starting ACE (or start at very low dose and watch carefully)
- ◆ Caution use in: renal insufficiency, RAS
- ◆ Cough
- ◆ Hyperkalemia
- ◆ My pick: they're all about the same
 - Differences in pharmacokinetics
 - Effects on "tissue" ACE ?

Adverse Effects

- ◆ Angioedema
- ◆ Rash
- ◆ Neutropenia
- ◆ Metallic taste
- ◆ Concurrent diuretic
- ◆ Cough
- ◆ Proteinuria
- ◆ Hyperkalemia
- ◆ Postural hypotension
- ◆ Renal artery stenosis

Angiotensin II Receptor Antagonists

- ◆ Mechanism of Action: Competitively, reversibly block AT-2 type 1 receptors



Angiotensin II Antagonists

- ◆ Efficacy equal to ACE-I
- ◆ Indication: ACE-I is indicated but unable to tolerate
- ◆ ACE-I's without the cough?
- ◆ Comparably priced to ACE-I's
- ◆ A lot more on the way

Combination ACE-I and ARB

- ◆ Combination tx appears to be more effective in reducing BP and proteinuria than either drug alone
- ◆ More “complete” inhibition of A-II effects

Calcium Channel Blockers

- ◆ Verapamil (Calan, Verelan, Covera-HS)
- ◆ Diltiazem (Cardizem, Dilacor, Cartia XT)
- ◆ Dihydropyridines (the “-ipines”)
 - 1st generation - e.g., nifedipine
 - 2nd generation - e.g., amlodipine

Calcium Channel Blockers

- ◆ MOA:
 - blocks Ca channels in myocardium and vasculature → vasorelaxation → ↓ SVR
- ◆ Patient selection
 - elderly, blacks = whites, angina, PVD, migraine px
- ◆ Caution: CHF, 2° or 3° heart block
- ◆ Anti-anginal
- ◆ Differ in side effect profiles
- ◆ Diuretic additive
- ◆ NOT protective post-MI
- ◆ Increase mortality ????

Adverse Effects

- | | |
|------------------------|------------------------------------|
| ◆ Headache | ◆ Flushing |
| ◆ Bradycardia (V/D) | ◆ Edema (DHP) |
| ◆ Dizziness | ◆ Reflex tachycardia (DHP) |
| ◆ Constipation (V) | ◆ AV conduction disturbances (V/D) |
| ◆ Postural hypotension | |
| ◆ GERD (DHP) | |

Calcium Channel Blockers

- ◆ Good in elderly, blacks = whites
- ◆ Anti-anginal
- ◆ Differ in side effect profiles
- ◆ Diuretic additive
- ◆ NOT protective post-MI
- ◆ Increase mortality ????
- ◆ My pick: Adalat CC, amlodipine

Alpha-1 Blockers

- ◆ Doxazosin (Cardura), Terazosin (Hytrin) are once-daily
- ◆ Prazosin (Minipress) - rarely used
- ◆ Lipid-lowering
- ◆ Also used for BPH
- ◆ First dose syncope (give HS)
- ◆ Caution: orthostatic hypotension
- ◆ Rather expensive
- ◆ Avoid in CHF (ALLHAT)

Alpha-1 Blockers

- | | |
|-----------------------|------------------------|
| ◆ Patient Selection | ◆ Adverse effects |
| – Good add on agents | – Syncope |
| – Lipid abnormalities | – Dizziness |
| – HTN and BPH | – Headache |
| | – Postural hypotension |
| | – Sexual dysfunction |
| | – ↑ HDL, ↓ LDL |

Central Alpha-2 Agonists

- | | |
|--------------|------------|
| ◆ Methyldopa | Clonidine |
| Guanabenz | Guanfacine |
- ◆ MOA: see classification of drug
 - ◆ 7-day patches (clonidine)
 - Rebound hypertension, may precipitate CVA, MI
 - ◆ CNS effects in elderly
 - ◆ Xerostomia a big reason for noncompliance
 - ◆ Patient selection:
 - compliance, add on therapy, cost, pregnancy

Others

- ◆ Direct Vasodilators
 - Hydralazine
 - Minoxidil
- ◆ Adrenergic Inhibitors
 - Reserpine
 - Guanethidine
 - Guanadrel
- ◆ Adverse effects
 - hypertrichosis
 - reflex tachycardia
- ◆ Adverse effects
 - postural hypotension
 - sexual dysfunction
 - depression

Alpha-Beta Blockers

- ◆ Products
 - Labetalol (Trandate, Normodyne)
 - Carvedilol (Coreg)
- ◆ Not used frequently in routine tx of HTN
- ◆ Severe, renovascular HTN?

Combinations

- ◆ Lotrel: amlodipine + benazepril
- ◆ Lexxel: felodipine + enalapril
- ◆ Teczem: diltiazem + enalapril
- ◆ Tarka: verapamil + trandolapril
- ◆ Not indicated as initial treatment
- ◆ Superior to either agent alone
- ◆ Niche yet to be defined
 - ACEI+CCA: less edema, reduces proteinuria

Special Situations

- ◆ **Blacks**
 - Best: diuretic, CCB
 - Avoid: ACEI, β -blockers
- ◆ **Women: ? thiazide**
- ◆ **Pregnancy**
 - Best: methyldopa, hydralazine
 - Avoid: ACEI, β -blockers (1st trim)

Special Situations

- ◆ **Elderly**
 - Best: diuretic, β -blocker
 - Avoid: vasodilators, central α_2 agonists, α -blockers
- ◆ **CAD: β -blockers (non-ISA), CCB**
- ◆ **CHF**
 - Best: ACE-I, vasodilators, β -blockers
 - Avoid: CCB, alpha-blockers

Special Situations

- ◆ **LVH: Avoid vasodilators**
- ◆ **Renal dz: loops, caution with ACEI**
- ◆ **DM**
 - Best: ACEI (+/- A-II blocker)
 - Avoid: β -blockers (if hypoglycemia is a concern)
- ◆ **COPD / Asthma**
 - Best: CCB (but may aggravate hypoxia)
 - Avoid: β -blockers

Drugs That Can Exacerbate HTN

- ◆ Oral contraceptives
- ◆ NSAIDs
- ◆ Caffeine, Nicotine
- ◆ Sympathomimetics
- ◆ MAO Inhibitors/Tyramine
- ◆ Licorice (glycyrrhizic acid)
- ◆ Steroids
- ◆ Cyclosporine
- ◆ Etoh
- ◆ Street drugs

HTN CRISES: Emergencies & Urgencies

- | | |
|-------------------------------|---------------------------|
| ◆ Emergencies | ◆ Urgencies |
| – Hypertensive encephalopathy | – Upper stage 3 HTN |
| – Intracranial hemorrhage | – HTN w/ optic disk edema |
| – Unstable angina | – Perioperative HTN |
| – Acute MI | |
| – Eclampsia | |

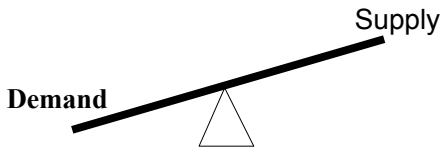
Emergencies & Urgencies

- | | |
|----------------------------------|--------------------|
| ◆ Emergencies | ◆ Urgencies |
| – ↓ by 25% max | – Clonidine usage |
| – then: 160/100 | – Captopril usage |
| – Avoid excessive falls | – Goal <110 DBP |
| | – Avoid nifedipine |
| – (See table 10 for agents used) | |

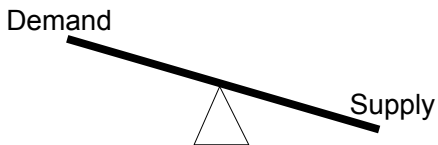
Treatment of Coronary Artery Disease

Michael A. Oszko, Pharm. D.

Myocardial Ischemia



Myocardial Ischemia Treatment Principle



Myocardial Ischemia

Demand

Heart Rate
Contractility
Blood Pressure

Supply

Arterial pO₂
Hemoglobin
Coronary Blood Flow

Coronary Artery Disease Primary Prevention

- ◆ Cessation of Cigarette Smoking
- ◆ Control of Blood Pressure
- ◆ Control of Cholesterol Levels
- ◆ Exercise
- ◆ Weight Control
- ◆ ? Hormone replacement therapy (HRT)

Coronary Artery Disease Secondary Prevention

- ◆ Hormone Replacement Therapy
 - HERS trial: no decrease in cardiac mortality
 - WHI: some evidence of *increased risk* in first two years, then no difference in cardiac mortality
- ◆ Post-menopausal women should not receive HRT for CVD prevention only

**Coronary Artery Disease
Treatment Options**

- ◆ Nitrates
- ◆ Beta Blockers
- ◆ Calcium Channel Blockers
- ◆ ASA
- ◆ HRT (?)

**Nitrates
Mechanism of Action**

- ◆ Reduce Cardiac Preload
- ◆ Dilate Coronary Arteries

**Nitrates
Chemical Entity**

- ◆ Nitroglycerin
- ◆ Isosorbide Dinitrate
- ◆ Isosorbide Mononitrate

Nitrates
Method of Administration

- Sublingual
- Immediate Release
- Sustained Release
- Paste
- Patch
- Intravenous

Nitrates
Key Features

- ◆ Nitrate Free Interval (8-12 hrs)
- ◆ Cost

Sublingual Nitroglycerin

- ◆ First Line Agent
- ◆ Acute Pain/Prophylaxis
- ◆ Patient Education Is Critical
- ◆ Must Keep Fresh Supply

Nitrate Free Interval

- ◆ ISDN: 0700; 1200; 1500
- ◆ ISMN: 7 hours apart (BID)
- ◆ Paste: 0700; 1200; 1500
- ◆ Patch: 12 hr. on; 12 hr. off

Beta Blockers Mechanism of Action

- ◆ Decrease Heart Rate
- ◆ Reduce Blood Pressure
- ◆ Decrease Contractility

Beta Blockers Differences

- ◆ β Selectivity
- ◆ ISA
- ◆ α Blocking Activity

**Beta Blockers
Limitations**

- ◆ Adverse Effects
- ◆ Contraindications

**Beta Blockers
Withdrawal of Treatment**

- ◆ Unstable Angina – Exercise Caution
- ◆ Limit Physical Activity
- ◆ Taper Over 10-14 Days

**Calcium Channel Blockers
Distinctly Different**

- ◆ Verapamil
- ◆ Diltiazem
- ◆ Nifedipine
- ◆ Bepridil

**Calcium Channel Blockers
Concerns**

Verapamil

Diltiazem

CHF

CHF

Bradycardia

Bradycardia

Constipation

**Nifedipine, et al
Concerns**

- ◆ Flushing
- ◆ Dizziness
- ◆ Peripheral Edema
- ◆ Avoid - short-acting

**Aspirin
Should be administered to all
Patients with at least one risk
factor unless an allergy to it exists!**



Effect of Agents on Myocardial Oxygen Demand

	Heart Rate	Contractility	BP
Nitrates	↑	○	↓
β Blockers	↓↓	↓	↓
Nifedipine	↑	○	↓
Verapamil	↓	↓	↓
Diltiazem	↓	↓	↓

Coronary Artery Disease Treatment Plan

1. Initiate Aspirin
2. Sublingual NTG
3. NTG vs. CCB vs. βB
4. Maximize Single Agent
5. Combination Treatment

Anti-Oxidants

- ◆ α -tocopherol (Vitamin E)
–No evidence of benefit
- ◆ Ascorbic acid (Vitamin C)
- ◆ Beta-carotene
- ◆ Ubiquinone (Coenzyme-Q)

Coronary Artery Disease
Agent Selection

- CHF ?
- PVD ?
- COAD ?
- DM ?
- Conduction Problems ?
- Age?
